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on Drugs and Therapeutics

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CYTOMEL AND TRIONINE

Liothyronine (Cytomel - S.K.F.; Trionine - Roche) – technically, triiodothyronine – is thyroxine less one of its four iodine atoms. Its action is much more rapid than that of desiccated thyroid or thyroxine, and it is promoted as "the preparation of choice" for the treatment of hypothyroidism. For some time, liothyronine appeared to offer great promise, and on the basis of a large volume of evidence, it was accepted by many as an important contribution to the treatment of hypothyroidism. Increasingly, however, questions have been raised about the value of this drug.

HOW IT'S SUPPOSED TO WORK - Experimental evidence has been offered to show that the body's tissues remove the fourth iodine atom from thyroxine and then utilize the converted triiodo compound. Because their tissues are unable to effect this conversion, it is claimed, some persons suffer from a syndrome called "metabolic insufficiency" or "hypometabolism." It is further claimed that despite normal serum cholesterol, normal protein-bound iodine, and normal radio-iodine uptake, these persons suffer from chronic fatigue, musculoskeletal aches and stiffness, nervousness, emotional instability and other symptoms. Supposedly the symptoms are refractory to desiccated thyroid but they respond dramatically when liothyronine is substituted.

The chemical evidence for the conversion of thyroxine to liothyronine in the tissues has been traced to a technical error (W. E. Lassiter and J. B. Stanbury, J. Clin. Endocr. and Metabolism, 18:903, 1958), and there is no proof that such a conversion takes place. Furthermore, despite a respectable volume of evidence, there has not been a single well-controlled investigation to support the entire concept of "metabolic insufficiency" and its cure with liothyronine. The symptoms of "metabolic insufficiency" are precisely the kind often seen in psychoneuroses and post-viral states (F. R. Keating, Jr., J. Clin. Endocr. and Metabolism, 18:531, 1958). (See also "The PBI Test and the Reader's Digest," below.) Spontaneous remission, normal variation in symptoms, and placebo effects readily account for the benefits attributed to liothyronine. To the extent that the symptoms are actually due to thyroid deficiency, the published reports fail to prove that the same results could not have been achieved with ordinary desiccated thyroid.

CASE REPORTS - Many of the case reports on liothyronine have a familiar ring. In these reports it appears that desiccated thyroid had been used without success; then liothyronine was introduced, with dramatic improvement. Over the years, similar dramatic improvement has been described in innumerable case reports on

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one new drug after another. In the absence of suitable controls, however, no one could be sure that it was the new drug that was responsible for the improvement.

It was precisely to guard investigators against self-delusion by just such "cures" that "double-blind" clinical testing was devised. And it is precisely with such vague and subjective symptoms as those of "metabolic insufficiency" that the safeguard of the well-controlled double-blind study is most necessary – and, unfortunately, most lacking.

It is claimed that liothyronine improves spermatogenesis and relieves menstrual and other female reproductive disorders. There is no sound evidence that liothyronine has any greater effect than thyroid (and evidence that the latter drug is of value in these conditions awaits confirmation by carefully controlled clinical investigation).

SPECIAL USES - Thanks to its rapid action, liothyronine does have special uses: (1) It should be used in the rare cases of myxedema coma, where the most rapid action possible is essential to save the patient's life. (2) Its rapid action can be useful in myxedema patients who need emergency surgery. (3) Its rapid action makes it useful as a diagnostic aid for hyperthyroidism; its failure to depress radioactive-iodine (I^{131}) uptake in the presence of hyperthyroidism can be determined in from two to five days whereas ordinary thyroid will take a week or so. In the treatment of hypothyroidism generally, however, its rapid – and brief – action is a disadvantage, not an advantage ("Hypothyroidism," Ingbar and Freinkel, "Disease-a-Month" series, September 1958, Year Book Publishers). With thyroid preparations, slow and prolonged action and gradual increase in dosage, rather than fast and brief action is in most circumstances a positive virtue. Liothyronine can be used for myxedema in carefully controlled microgram dosage in place of desiccated thyroid, but its action is so brief that the omission of two or three doses may lead to relapse. Since liothyronine is not bound to serum proteins, it does not elevate and it may lower the serum protein-bound iodine, which therefore fails as a guide to dosage – a peculiarity that can lead to dangerous overdosage if it is not taken into account. Furthermore, its rapid action makes it a much more serious hazard than the slower acting desiccated thyroid in patients with cardiovascular disorders.

LIOTHYRONINE IN DIAGNOSIS - The suggestion that liothyronine be used as a diagnostic tool for hypothyroidism is an unfortunate one. If the patient feels better after taking it, that is supposed to indicate hypothyroidism, but it may indicate only that liothyronine is a good placebo. Wide use of the drug in this way would doubtless result in the prolonged dosing of many normal patients with liothyronine. (The cost of Cytomel to the patient is about 3-1/2¢ per 25-mcgm. tablet. Equivalent dosage of Thyroid USP (1 gr.) costs about a cent.)

THE CHOICE AND COST OF THYROID PREPARATIONS

Thyroid USP can be put up in tablets, coated or uncoated, odorless or not odorless; or in gelatin capsules. Provided the finished product meets all USP requirements, it is unimportant whether it is called "Tabloids," "Enseals," "Proloids," or anything else; it all comes to the same thing: there is no evidence that anything can be done to thyroid to make it clinically superior to Thyroid USP.

The U. S. Pharmacopeia is the supreme authority for specifying the identity and potency of drugs. It provides carefully developed standards which are subject to revision every five years. It sets forth explicitly the attributes of a preparation of desiccated thyroid, and no preparation may be labeled Thyroid USP unless it meets USP standards. In fact, if the preparation moves in interstate commerce, federal law requires that it meet USP standards if it purports to be desiccated thyroid whether or not "USP" appears on the label. If any manufacturer found ways of giving desiccated thyroid useful new attributes leading to greater clinical dependability, the USP specification would be changed to include such attributes; such changes have been made with many remedies from time to time.

THE CAUSE OF FAILURE - Because treatment with thyroid is often clinically disappointing, it is tempting to regard the failure as due to faults of the preparation used, and to turn to products made with "better methods of extraction," or "better standardization," or other supposed improvements. According to the Federal Food and Drug Administration, substandard USP thyroid preparations are rarely encountered. Thus failures in clinical performance are not likely to be due to the preparation used. Improved clinical performance is more likely to come from more accurate diagnosis and careful adjustment of dosage in accordance with clinical changes. All that can be said of the "better" preparations is that they contain thyroidal iodine in an amount not more nor less than the official limits, and Thyroid USP by whatever name can be expected to yield substantially the same clinical results. While thyroxine and levothyroxine (Synthroid - Travenol Labs.) are occasionally prescribed, especially by pediatricians, it is generally believed that they offer no significant advantage over such a well-standardized product as Thyroid USP. They have the disadvantage of much higher price.

There is some belief that thyroid tablets quickly lose potency when they are stored. Careful laboratory tests disprove this belief. A report from one laboratory showed that uncoated Thyroid USP retains its biologic activity for at least 3-1/2 years and that coated tablets retain full activity for over 10 years (JAMA, 167:101, 1958). Except for this generally unnecessary addition to shelf life, however, coating adds no clinical benefits to plain thyroid. The cost to the druggist (Drug Topics Red Book 1959) of 1000 one-grain Thyroid USP tablets ranges from $1 (Lit) and $1.05 (American) to $3.78 (Armour). Tabloids cost the druggist $3.36 per thousand, and Proloids, $3 for 500. Thyroxin Fraction Tablets (0.2 mg.) cost the druggist $2.75 per hundred, levothyroxine (0.1 mg.) costs $1 per hundred ($8 per 1000), and Cytomel (25 mcgm.), $2.28 per hundred.

THE PBI TEST AND THE READER'S DIGEST

Oversimplification is the rule in much popular medical writing, and the physician often has the problem of explaining to a patient that the diagnosis of a condition or its treatment isn't quite so simple as it was made to appear. By this time many physicians will have had such explaining to do as the result of a February Reader's Digest article asserting that many or most of the "several million men – and an even larger number of women – [who] wake up feeling unaccountably tired, irritable and depressed" are suffering from "partial hypothyroidism" or slight underactivity of the thyroid gland. The article suggests that the protein-bound iodine (PBI) blood test is the sure way for the doctor to discover "partial hypothyroidism" and to start the patient on the road to recovery.

MANY ARE TIRED - It is true that some patients, particularly in the older age groups, are "tired, irritable and depressed" and have other "vague and varying" symptoms because of hypothyroidism. But they probably account for only a small fraction of those who suffer from fatigue, irritability and depression. Such symptoms may occur at times in perfectly normal people. It doesn't take hypothyroidism to create them in the harried mother of a brood of young children. Obese persons who overeat and never exercise, and whose obesity has nothing to do with thyroid function, often display these symptoms. They are also quite common in many emotional and physical disorders.

As for the PBI test, it can, as the Digest points out, be a much more accurate and reliable test of thyroid function than the basal metabolism test. But there are two hitches, and they are serious. For one thing, the possibility of technical error in the performance of the PBI test is very great – far greater than the margin of error in the performance of blood-sugar, blood urea, and other well-established laboratory tests. The Digest article says that in 250 medical centers and clinical laboratories "technicians have been trained to perform the test." That may be true, but how accurately they do it is another matter. Not long ago, the U. S. Army Medical Corps sent samples of the same blood for PBI to a group of laboratories scattered throughout the country. The readings were so variable that the patient would have been diagnosed as hypothyroid by some laboratories, normal by some, and hyperthyroid by others. Some tests are accurate; some are not. Physicians can never afford to accept the results of PBI tests (or any other tests) blindly; they always have to look at the total clinical picture and use their own judgment. (Despite its well-known limitations, the basal metabolism test continues to serve a useful function in medical practice.)

CAUSES OF FALSE VALUES - And this brings us to the second hitch. The PBI can give false values even when correctly performed. For example, it can mask genuine hypothyroidism by giving false high values for a considerable period in a patient who had received an organic iodine injection or instillation: for about two to three weeks (with some dyes very much longer) after an intravenous pyelogram; for three to twelve months (with at least one dye, for many years) after a gallbladder x-ray; and up to several years after a bronchogram. The use of vaginal suppositories containing organic iodine radicals for the treatment of trichomonas infections can affect the PBI. While iodized salt, potassium-iodide medication, "health" foods containing kelp, Lugol's solution, some cough syrups, and other preparations containing iodine are less likely to affect the reading, performance of the test for varying periods after such preparations have been used may introduce some error. Furthermore, low PBI values can be found in persons with normal thyroid function if they have subnormal serum proteins, if they have used mercurial diuretics within the previous 24 hours, if they had recently been taking thyroid or if they are or have recently been on steroid therapy. As a matter of fact, it has been found that the PBI may be low (or high) in some normal persons for no known cause.

While the PBI – accurately performed – is the best single test of thyroid function, even when accurately done, it can be misleading. Add the chance of inaccurate performance, and it clearly cannot be relied on to pinpoint borderline cases, as urged in the Digest article.

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